

Study of Anti Ulcer Activity of Sodium Metavanadate on Alcohol and Pylorus Ligation Induced Gastric Ulcers in Rats

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The present study was designed to evaluate the effects of sodium metavanadate against experimentally-induced gastric ulcers. In an attempt to establish the antiulcer effect and its mechanism of action, sodium metavanadate (3, 5 mg/kg, i.p.) was studied in ethanol and pylorus ligation-induced gastric ulcer models. Sodium metavanadate significantly reduced ulcer index in both the ulcer models. Besides it showed significant reduction in total acid output along with significant rise in total carbohydrates and mucin activity in gastric juice in pylorus ligation model. Therefore, it is suggested that sodium metavanadate possesses significant antiulcer activity. The probable mechanisms for its antiulcer effect can be attributed to decrease in acid secretion and increase in mucoprotective substances.

Trace elements present in human and animal body are known to have great importance in their life. Various disorders are associated with less and/or high intake of such trace elements. Vanadium is among the lowest trace elements in mammals¹. It has also been studied for its antidiabetic activity and regulatory effects on ion transports^{2,3}. In several reports, it has been shown to inhibit H⁺-transport through GI mucosa^{4,5}. It has been also found to inhibit acid secretion by gastric glands^{6,7}. Although nutritional essentiality has been established for the chicken and the rat, the physiological role of vanadium in human beings remains unknown. Thus, the present study was designed to evaluate the effects of vanadium against ethanol and PL -induced gastric ulcers in rats.

Wistar rats weighing 150-200 g were selected. They were fed standard chow diet and water, under the standard conditions 12 h dark-light cycle, 60±10 humidity, and temperature 21±1°. The animal experiments were performed according to laboratory guidance of our institution. Animals were randomly divided in to various groups of six in each group. Before experiment, animals were fasted for 24 h. Coprophagy was prevented by keeping the animals in the cages with grating floor.

Ethanol-induced gastric mucosal damage⁸ was produced by administering orally 1 ml of absolute

alcohol to 24 h fasted rats. In the treatment group 24 h fasted rats received sodium metavanadate (3 and 5 mg/kg, ip) 30 min prior to ethanol ingestion. The control group received distilled water. Two hours after the ethanol administration, all animals were sacrificed by ether overdose. Stomachs were removed, opened along the greater curvature, and ulcer indices were determined⁹. Glandular portion of stomach was subjected to measurement of free radical activity measured as thiobarbituric acid reacting substances (TBA-RS)¹⁰.

Pylorus ligation was carried out on 24 h fasted rats as per method under ether anesthesia and 19 h after the PL, stomachs were opened and ulcer indices determined^{9,11}. Gastric content was subjected to biochemical analysis for total acidity¹², total acid output¹² (TAO), pepsin activity¹³, total carbohydrates¹⁴ (TC), and protein contents¹⁵ (PR). Mucin activity (TC/PR ratio) was also determined. Control and treated animals were administered vehicle and sodium metavanadate (3 and 5 mg/kg, ip) immediately after the pylorus ligation, respectively. Results were expressed as mean±SEM and analyzed for statistically significant difference using unpaired student's t-test. $p < 0.05$ were considered significant.

For the rats with ethanol induced gastric mucosal damage, linear hemorrhagic lesions were observed in the glandular portion of stomachs of control group. Sodium metavanadate (3 and 5 mg/kg, i.p.) showed significant decrease ($p < 0.05$) in the ulcer index when compared with control group (Table 1).

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TABLE 1: EFFECT OF SODIUM METAVANADATE ON ULCER INDEX AND LIPID PEROXIDATION (TBA-RS) IN ETHANOL-INDUCED GASTRIC ULCERS IN RATS

Parameter	Control	Sodium metavanadate (3 mg/kg, i.p.)	Sodium metavanadate (5 mg/kg, i.p.)
Ulcer index	2.9552±0.455	0.7241±0.0998*	0.2648±0.558*
TBA-RS (nmol/g wet tissue)	3.1411±0.7828	1.8517±0.0558	3.66±0.6431

N=6 in each group, * $p < 0.05$, when compared with the control

For pylorus ligation-induced gastric ulcers, there were linear lesions and petechies in glandular portions of the stomach along with dark black lesions of circular hemorrhagic type in rumenal area in control group of animals. In treated group, sodium metavanadate (3 and 5 mg/kg, ip) significantly ($p < 0.05$) decreased the ulcer index when compared with the control group. Besides significant reduction in total acid output, significant increase in total carbohydrates and TC/PR ratio were also observed. Sodium metavanadate only at higher dose (5 mg/kg, ip) showed significant reduction in pepsin activity (Table 2).

Although nutritional essentiality has been established for the chicken and rat, the physiological role of vanadium remains unknown. Intracellular deficiency of trace elements (eg. vanadium, lithium) has been shown in diabetes, obesity, and hypertension¹⁶. In France, vanadium was widely used for the treatment of anemia, tuberculosis, chronic rheumatism, and diabetes¹⁷.

Ethanol damages the plasma membrane and leads to intracellular accumulation of sodium and water by increasing the membrane permeability. These changes ultimately cause cell death and gastric mucosal exfoliation¹⁸. Ethanol is also known to release the endogenous ulcerogenic mediators. These could precipitate mucosal injury either by causing vascular changes like mucosal edema and increased mucosal

permeability¹⁹ or by non-vascular effects like mucus depletion and enzyme release in the stomach²⁰. In our study, sodium metavanadate significantly reduced mucosal damage induced by ethanol, which suggests that sodium metavanadate like other metal zinc and copper may strengthen the gastric mucosal barrier. Several reports suggest the major role of mucosal vasculature in ethanol induced lesions, mostly affected by prostaglandins. Vanadium is known to stimulate prostaglandin production by increasing the release of arachidonic acid and its conversion into prostaglandin²¹. Data from our laboratory study has also shown the relation between vanadium and prostaglandin as vanadium decreased ulceration in NSAIDs-induced gastric ulcers in rats. The protective role of nitric oxide has been well-established in ethanol-induced gastric ulcers. It may be possible that vanadium may increase nitric oxide content as it has been reported to increase the eNOS and iNOS activity in several tissues²². Vanadium also dilates rat mesenteric vascular bed through the release of the endogenous vasodilator, NO²³.

Gastric secretion plays an important role in gastric ulcer pathogenesis²⁴. Increased synthesis of nucleic acids and increased metabolism of carbohydrates and thereby exhaustion of carbohydrates and compensatory mechanisms could be responsible for pylorus ligation induced gastric ulcers²⁵. Moreover, one of the essential criteria to determine the status of mucus resistance/barrier is the state of mucus secretion. This mucus consists of mucin type glycoproteins, which can be determined by ratio of total carbohydrates to protein in gastric juice. These high molecular weight glycoproteins are mainly responsible for viscous and gel forming characteristic of the mucus. Increased mucus secretion by the gastric mucosal cells can prevent gastric ulceration by several mechanisms, including lessening of stomach wall friction during

TABLE 2: EFFECT OF SODIUM METAVANADATE ON SECRETORY PARAMETERS IN PYLORUS LIGATION-INDUCED GASTRIC ULCER MODEL

Parameter	Control	Sodium metavanadate (3 mg/kg, i.p.)	Sodium metavanadate (5 mg/kg, i.p.)
Ulcer index	0.788±0.1214	0.316±0.05*	0.2733±0.1694*
Volume of secretion (ml/100 g/19 h)	3.355±0.6688	2.305±0.4754	2.074±0.405
Total acid out put (μEq/100 g/19 h)	18.22±4.339	9.054±2.349*	6.775±1.901*
Pepsin activity (μg/ml)	731.61±39.077	564.8±98.89	534.185±116.89*
Total carbohydrates (TC) (μg/ml)	202.71±21.44	393.94±49.69*	466.13±21.65*
Protein (PR) (μg/ml)	579.63±29.20	444.16±77.59	445.70±74.26
Mucin activity (TC/PR)	0.393±0.043	0.845±0.151*	1.16±0.274*

N=6 in each group. * $p < 0.05$ when compared with the control group

peristalsis and gastric contractions, improving the buffering of acid gastric juice and by acting as an effective barrier to back diffusion of H^+ ions²⁶. In the present study, sodium metavanadate showed reduction in gastric acid secretion along with enhancement of mucin activity. These results can be correlated with the previous studies associated with inhibitory effect of vanadium on H^+/K^+ -ATPase in in alicals models^{4,5}.

This study suggests the protective role of vanadium in pylorus ligation induced gastric ulcers, which may be mediated by suppressing aggressive factors like gastric acid secretion and by maintaining the integrity of gastric mucosal barrier as evident from ethanol induced gastric ulcer model and enhanced mucin activity (measured as TC/PR ratio) in PL-induced gastric ulcer model.

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